WHAT IS CLAIMED IS:

1. A method for producing a protein having an antithrombotic activity, which comprises replacing, in a protein that has an amino acid sequence having a homology of not less than 30% to the amino acid sequence of SEQ ID NO: 1 and forms a higher order structure composed of a first β strand (β1), a first α helix (α1), a second α helix (α2), a second β strand (β2), a loop, a third β strand (β3), a fourth β strand (β4) and a fifth β strand (β5) in this order from the amino terminus, at least one amino acid residue in a region from α2 to β2 and/or a region from β3 to β4 so that electric charge of the amino acid residue is changed towards positive direction.

2. The method according to Claim 1, wherein at least one acidic amino acid residue in the region from α2 to β2 and/or the region from β3 to β4 is replaced with a neutral amino acid residue to change electric charge of the amino acid residue towards positive direction.

3. The method according to Claim 1 or 2, wherein the protein originates from *Crotalus horridus horridus*.

4. The method according to any one of Claims 1 to 3, wherein the region from α2 to β2 in the protein corresponds to the sequence of the amino acid numbers 47 to 72 in the amino acid sequence of SEQ ID NO: 1 and the

region from β3 to β4 corresponds to the sequence of the amino acid numbers 94 to 111 in the amino acid sequence of SEQ ID NO: 1.

5. The method according to Claim 4, wherein at least one acidic amino acid residue of which α carbon atom exists within 10 Å from the α carbon atom of the arginine residue of the amino acid number 103 in the amino acid sequence of SEQ ID NO: 1 is replaced with a neutral amino acid residue.

6. The method according to Claim 5, wherein the acidic amino acid residue is at least one residue selected from the aspartic acid residue of the amino acid number 54, the aspartic acid residue of the amino acid number 101 and the glutamic acid residue of the amino acid number 106 in the amino acid sequence of SEQ ID NO: 1.

7. The method according to any one of Claims 1 to 6, which further comprises deleting a region containing the loop structure existing between β2 and β3 in such a manner that the higher order structures of β2 and β3 are maintained, or replacing the region with one or more amino acid residue(s) in a number required to maintain the higher order structures of β2 and β3, said amino acid residue(s) being selected from the group consisting of a glycine residue, an alanine residue, a serine residue and a cysteine residue.

8. The method according to Claim 7, wherein the region containing the loop structure existing between β2 and β3 is replaced with an amino acid sequence composed of four glycine residues.

9. The method according to any one of Claims 1 to 8, which further comprises bonding a polyoxyalkylpolyol group to the protein.

10. The method according to Claim 9, wherein the protein contains a cysteine residue corresponding to a cysteine residue of the amino acid number 81 in the amino acid sequence of SEQ ID NO: 1, and the polyoxyalkylpolyol group is bonded to said cysteine residue.

11. The method according to Claim 9 or 10, wherein the polyoxyalkylpolyol group is a polyethylene glycol group.

12. A protein having an antithrombotic activity, which has an amino acid sequence showing a homology of not less than 30% to the amino acid sequence of SEQ ID NO: 1 and forms a higher order structure composed of a first β strand (β1), a first α helix (α1), a second α helix (α2), a second β strand (β2), a loop, a third β strand (β3), a fourth β strand (β4) and a fifth β strand (β5) in this order from the amino terminus, and wherein

at least one amino acid residue in a region from α2 to β2 and/or a region from β3 to β4 is replaced so that electric charge of the amino acid residue is changed towards positive direction, said protein being the following (a) or (b):

(a) a protein, in which the region from α2 to β2 has the sequence of the amino acid numbers 47 to 72 in the amino acid sequence of SEQ ID NO: 1 and the region from β3 to β4 has the sequence of the amino acid numbers 94 to 111 in the amino acid sequence of SEQ ID NO: 1;

(b) the protein according to (a), in which substitution, insertion or deletion of one or several amino acid residues is included in the region from α2 to β2 having the sequence of the amino acid numbers 47 to 72 in the amino acid sequence of SEQ ID NO: 1 and/or the region from β3 to β4 having the sequence of the amino acid numbers 94 to 111 in the amino acid sequence of SEQ ID NO: 1.

13. The protein according to Claim 12, which comprises an amino acid sequence of the following (A) or (B):

(A) the amino acid sequence of the amino acid numbers 47 to 111 in the amino acid sequence of SEQ ID NO: 1;

(B) the amino acid sequence according to (A), in which the cysteine residue of the amino acid number 81 in the amino acid sequence of SEQ ID NO: 1 is replaced with an alanine residue.

14. The protein according to Claim 12, which has the amino acid sequence in which a region containing the loop structure existing between β2 and β3 is deleted in such a manner that the higher order structures of β2 and β3 are maintained, or the region is replaced with one or more amino acid residue(s) in a number required to maintain the higher order structures of β2 and β3, said amino acid residue(s) being selected from the group consisting of a glycine residue, an alanine residue, a serine residue and a cysteine residue.

15. The protein according to Claim 14, wherein the region containing the loop structure existing between β2 and β3 is replaced with an amino acid sequence composed of four glycine residues.

16. The protein according to any one of Claims 12 to 15, wherein at least one acidic amino acid residue of which α carbon atom exists within 10 Å from the α carbon atom of the arginine residue of the amino acid number 103 in the amino acid sequence of SEQ ID NO: 1 is replaced with a neutral amino acid residue.

17. The protein according to Claim 16, wherein the acidic amino acid residue to be replaced is composed of at least one residue selected from the aspartic acid residue of the amino acid number 54, the aspartic acid of the amino acid number 101 and the glutamic acid residue of the amino acid number 106 in the amino acid

sequence of SEQ ID NO: 1.

18. The protein according to any one of Claims 12 to 17, wherein the protein is bonded to a polyoxyalkylpolyol group.

19. The protein according to Claim 18, wherein the protein contains a cysteine residue corresponding to a cysteine residue of the amino acid number 81 in the amino acid sequence of SEQ ID NO: 1 and the polyoxyalkylpolyol group is bonded to said cysteine residue.

20. The protein according to Claim 18 or 19, wherein the polyoxyalkylpolyol group is a polyethylene glycol group.

21. A DNA coding for the protein as defined in any one of Claims 12 to 17.

22. A method for producing the protein as defined in any one of Claims 12 to 17, which comprises steps of culturing a host microorganism transformed with the DNA according to Claim 21 and collecting a protein encoded by the DNA from a culture.

23. A method for producing the protein as defined in any one of Claims 18 to 20, which comprises steps of culturing a host microorganism transformed with the DNA

as defined in Claim 21, collecting a protein encoded by the DNA from a culture and bonding a polyoxyalkylpolyol group to the collected protein.

24. A drug comprising the protein as defined in any one of Claims 12 to 20 as an active ingredient.